

a 2-cephem or a 3-cephem system, and where the substituent(s)  $R^4$  when other than hydrogen may replace any of the hydrogen atoms bonded to carbon atoms in the side chain.

### **REMARKS**

Claims 1-18 and 21-24 are pending in the application. In the Office Action dated December 10, 2002, The Examiner has rejected Claims 1-18 and 22-24 under 35 U.S.C. §112, second paragraph and Claims 1-18 and 24 under 35 U.S.C. §112, first paragraph. Additionally, the Examiner has objected to Claims 2 and 4-20 under 37 C.F.R. §1.75(c).

This response addresses each of the Examiner's rejections. Accordingly, the present application is in condition for allowance. Favorable consideration of all pending claims is respectfully requested.

The Examiner has rejected Claims 1-18 and 22-24 under 35 U.S.C. §112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, pointing out that the last line of Claim 1 provides for an optional step of "forming the carboxylate salt of said compound of Formula III," the Examiner has alleged that this makes no sense in light of the definition of  $R^3$ . In response, applicants have clarified Claim 1 to specify that formation of the carboxylate salt is an option only when  $R^3 = \text{hydrogen}$  (*i.e.* when  $\text{CO}_2R^3$  is free carboxyl). It is well known in the art that carboxyl groups form carboxylate salts and that protected carboxyl groups do not. No new matter has been added.

Additionally, the Examiner has alleged that "3-cephem" is not correct in Claim 22 because X can be methylene as well as sulfur. Additionally, the Examiner has noted that Claim 23 has a period in the middle of the claim. Further, the Examiner has noted that Claim 23 refers

to Formula III but does not define it. In response, applicants have amended Claims 22 and 23 to correct these alleged deficiencies.

With regard to the correction of Claim 23, the structure of Formula III and the definitions of its substituents have been imported from Claim 1, as amended. No new matter has been added.

Further, the Examiner has rejected Claims 1-18 and 24 under 35 U.S.C. §112, first paragraph, alleging that the specification does not reasonably provide enablement for either the amended definition of  $R^3$  (as a protecting group, no longer modified by the phrase “readily removable”) or for  $R^4=OH$ . The Examiner admits that the specification is enabling for most substituents.

In response, applicants note that the phrase “readily removable” was previously deleted in an effort to comply with the Examiner’s recommendation. Applicants had interpreted the Examiner’s rejection of the phrase “readily removable” as based on the notion that only groups that are readily removable would be considered in the art to be protecting groups. Continuing their effort to comply, applicants have inserted the term “suitable”. Applicants submit that the term “suitable” is supported by the recitation “readily removable”, as originally filed. In support of this submission, applicants attach hereto brief discussions of protecting groups from two well-established texts in Organic Chemistry (Smith, Organic Synthesis, Chapter 7, Protecting Groups, 7.1, McGraw-Hill, Inc., (1994); Introduction to Organic Chemistry, 4<sup>th</sup> Ed. 451-452, Streitwieser, Heathcock, Kosower, Macmillan (1992)). The recognized textbook “good” protecting group is said to be “easily introduced and removed” and “conveniently removed.” In the Smith text, an appropriate protecting group is characterized as one which is “easily removed, in high yield.” Applicants respectfully submit that the

development and use of protecting groups is fundamental to the art of synthetic organic chemistry and that a person skilled in that art would be able to choose or develop a suitable protecting group without undue experimentation. No new matter has been added.

In response to the rejection with respect to substituent R<sup>4</sup>, solely in an effort to advance the prosecution of the subject application, applicants have amended Claim 1 to omit hydroxy as a possible substituent R<sup>4</sup>. Applicants reserve the right to pursue this subject matter in a continuation application.

Applicants submit that in view of the foregoing amendments, the rejections under 35 U.S.C. §112, first and second paragraphs, are overcome. Accordingly, withdrawal thereof is respectfully requested.

Additionally, the Examiner has objected to Claims 4-20 under 37 C.F.R. §1.75(c) as allegedly in improper dependent claim form. Initially, applicants respectfully note that Claims 19 and 20 were cancelled in the applicants' previous response and are therefore not pending in the application. With regard to Claims 4-18, applicants respectfully submit that as a result of the corrections in the previous Office Action, these claims currently reflect proper claim form. Specifically, applicants respectfully point out that both Claim 8 and Claim 11 depend on "Claim 1 or 2" neither of which is multiply dependent. Accordingly, applicants respectfully request that the Examiner withdraw the objection under 37 C.F.R. §1.75(c).

Additionally, the Examiner has objected to Claim 2 as allegedly failing to further limit the subject matter of the previous claim. Claim 2 specifies that CO<sub>2</sub>R<sup>5</sup> is CO<sub>2</sub>R<sup>3</sup> where CO<sub>2</sub>R<sup>3</sup> is a carboxyl group, a protected carboxyl group or a carboxylic acid salt. Applicants respectfully submit that Claim 2 further limits the subject matter of Claim 1 in that Claim 2 specifies that the carbon-carbon double bond is in the 3-position whereas Claim 1 allows the

double bond to be in either the 2-position or the 3-position. Further, in response to the Examiner's allegation that "Claim 2 enhances the carboxylate salt which is not provided for in Claim 1", applicants respectfully direct the Examiner's attention to paragraph 3 of the Remarks section of the previous response, in which applicants specifically note that the possibility that  $\text{CO}_2\text{R}^3$  is a carboxylate salt is retained in Claim 1, by means of the final phrase of Claim 1 "and optionally forming the carboxylate salt of said compound."

Accordingly, the objection to Clams 4-20 under 37 C.F.R. §1.75(c) is overcome and withdrawal thereof is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Thus, in view of the forgoing amendments and remarks, the present application is in condition for allowance.

Respectfully submitted,



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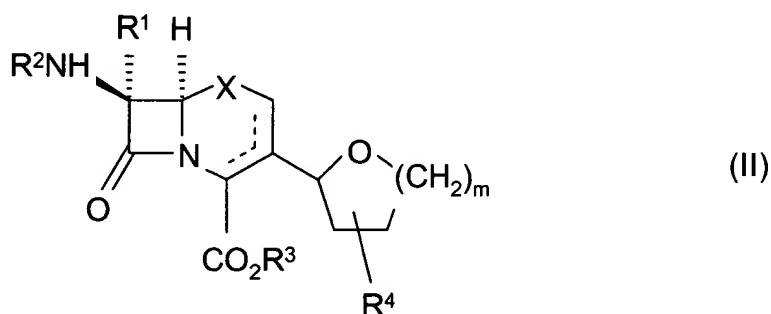
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**“VERSION WITH MARKINGS SHOWING CHANGES MADE”****IN THE CLAIMS:**

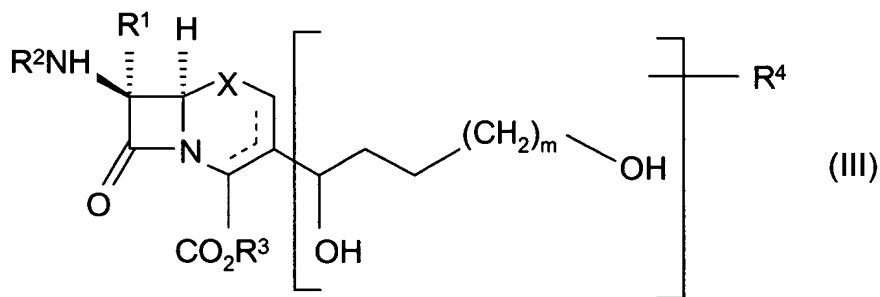
Claims 1, 11, 21-23 have been amended as follows:

1. (Twice Amended) A process for the preparation of a compound of formula

(II):



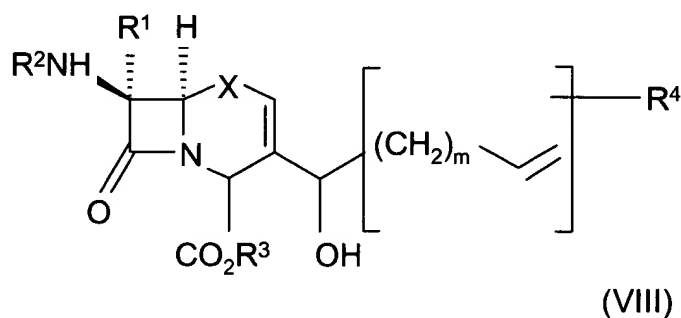
comprising cyclizing a compound of formula (III):



wherein in formulae (II) and (III), R<sup>1</sup> is hydrogen, methoxy or formamido; R<sup>2</sup> is an acyl group; R<sup>3</sup> is hydrogen or a suitable carboxy protecting group; R<sup>4</sup> represents hydrogen or up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, ~~hydroxy~~, halogen, amino, alkylamino, acylamino, dialkylamino, CO<sub>2</sub>R, CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub> (where R is hydrogen or C<sub>1-6</sub> alkyl), aryl and heterocyclyl, which may be the same or different; X is S, SO, SO<sub>2</sub>, O, or CH<sub>2</sub>;

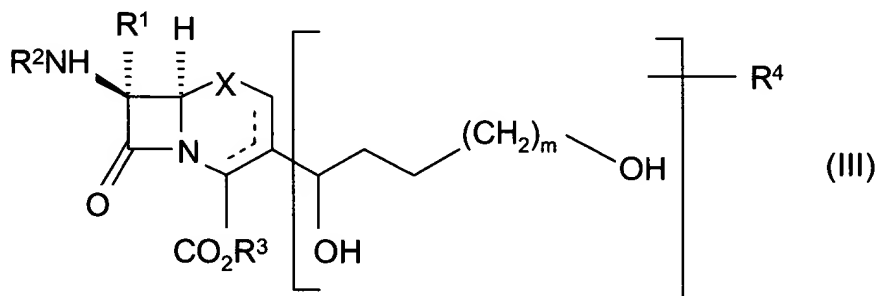
and m is 1 or 2; and the dotted line indicates that the compounds (II) and (III) may be a 2-cephem or a 3-cephem system, and where in formula (III) the substituent(s)  $R^4$  when other than hydrogen may replace any of the hydrogen atoms bonded to carbon atoms in the side chain, and, when  $R^3$  is hydrogen, optionally forming the carboxylate salt of said compound of formula III.

11. (Twice Amended) The process according to Claim 1 or 2, wherein the compound of formula III is prepared by coupling a compound of formula (IV) (as defined in claim 10) with an organometallic or boronate reagent to form a compound of formula (VIII):



and wherein said compound of formula VIII is then hydroxylated to form a compound of formula III, where  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , m, and X are as defined with respect to formula (III).

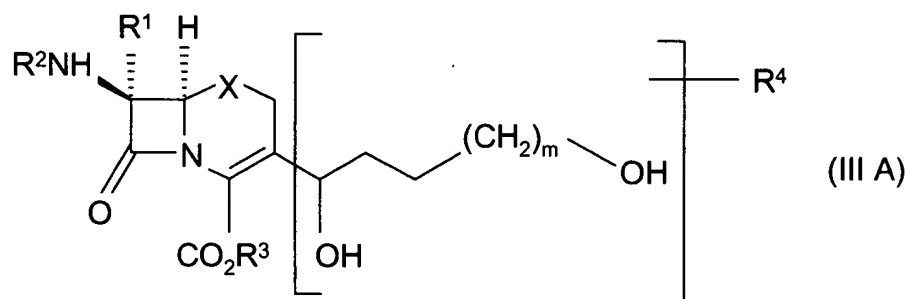
21. (Twice Amended) A compound of formula (III),



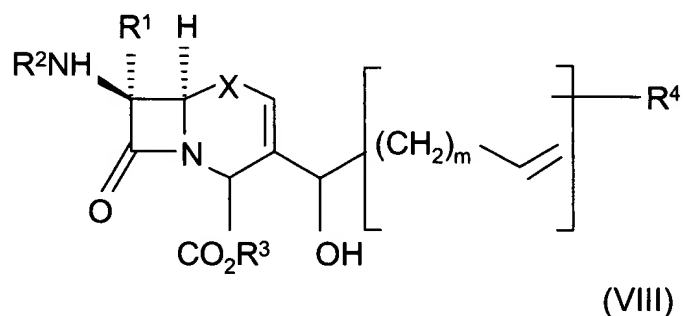
wherein  $R^1$  is hydrogen, methoxy or formamido;  $R^2$  is an acyl group;  $R^3$  is hydrogen or a suitable carboxy protecting group;  $R^4$  represents hydrogen or up to four

substituents selected from alkyl, alkenyl, alkynyl, alkoxy, ~~hydroxy~~, halogen, amino, alkylamino, acylamino, dialkylamino, CO<sub>2</sub>R, CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub> (where R is hydrogen or C<sub>1-6</sub> alkyl), aryl and heterocyclyl, which may be the same or different; X is S, SO, SO<sub>2</sub>, O, or CH<sub>2</sub>; and m is 1 or 2; and the dotted line indicates that the compound may be a 2-cephem or a 3-cephem system, and where the substituent(s) R<sup>4</sup> when other than hydrogen may replace any of the hydrogen atoms bonded to carbon atoms in the side chain.

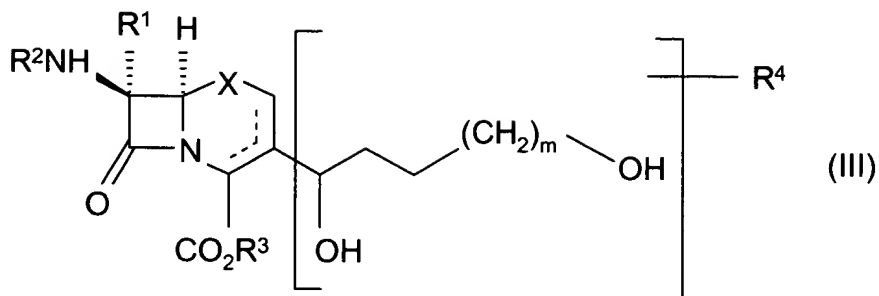
22. (Amended) The compound according to Claim 21, wherein the compound is a ~~3-cephem system, (~~ compound of formula IIIA).



23. (Amended) A compound of formula VIII,



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and m are defined with respect to formula III[.] ,



wherein  $R^1$  is hydrogen, methoxy or formamido;  $R^2$  is an acyl group;  $R^3$  is hydrogen or a carboxy protecting group;  $R^4$  represents hydrogen or up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, halogen, amino, alkylamino, acylamino, dialkylamino,  $\text{CO}_2\text{R}$ ,  $\text{CONR}_2$ ,  $\text{SO}_2\text{NR}_2$  (where R is hydrogen or  $\text{C}_{1-6}$  alkyl), aryl and heterocyclyl, which may be the same or different; X is S, SO,  $\text{SO}_2$ , O, or  $\text{CH}_2$ ; and m is 1 or 2; and the dotted line indicates that the compound may be a 2-cephem or a 3-cephem system, and where the substituent(s)  $R^4$  when other than hydrogen may replace any of the hydrogen atoms bonded to carbon atoms in the side chain.